

Study NM14185

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This was a two-year multicenter, randomized, placebo-controlled U.S. study. After completing a 4-week placebo lead-in, patients who were at least 75% compliant with the dosing regimen were randomized (3:1, orlistat:placebo) into 4 treatment groups with year 1/year 2 treatment of 1. 120 mg orlistat tid/120 mg orlistat tid, 2. 120 mg orlistat tid/60 mg orlistat tid, 3. 120 mg orlistat tid/placebo, and 4. placebo/placebo. From the start of the placebo lead-in, patients were on a mildly hypocaloric diet (30% of calories as fat). Patients who completed the first 52 weeks of treatment with at least 75% compliance with their dosing regimen were continued into the second year of treatment in which patients followed an eucaloric diet.

The objectives of the study were 1. to evaluate the long-term weight **control** effect of orlistat among the four treatment groups (placebo/placebo, 120mg/120mg, 120mg/60mg, 120mg/placebo), 2. to compare the effects on body weight change during the second year of 120 mg orlistat tid, 60 mg orlistat tid, or placebo tid in combination with a weight maintenance diet in patients who were treated with 120 mg orlistat tid and a hypocaloric diet for the first year, and 3. to determine the weight loss effect of 120 mg orlistat tid compared to placebo tid over a one year period in combination with a hypocaloric diet.

The following is a display of the overall design of the study and the number of patients entering and completing in each treatment phase.

Days	Inc/Exc		Baseline randomization		365	730
	-49	-28	1			
	screen	Placebo lead-in	Year One		Year Two	
	(1187)	(892)	(224) Placebo (138)	(133) Placebo (97)	(138) Placebo (95)	(152) Orlistat 60 mg (102)
			Orlistat 120 mg (668)	(458)	(153) Orlistat 120 mg (109)	
		Total (Percent)	892	596 (67%)	576	403 (45%)

One of the 19 participating centers (Center 12054) withdrew from

the study. The center enrolled 10 patients among which 8 were screen failures and 2 entered the placebo lead-in. A total of 1187 patients at 18 centers were entered in the 4-week placebo lead-in period. The 892 patients (75%) who completed the lead-in period were stratified into 2 strata (placebo lead-in weight loss ≤ 2.0 Kg or > 2.0 Kg) and randomized 668 on the orlistat 120 mg tid and 224 on placebo tid. In year one, four patients in the orlistat group and one in the placebo group were excluded from the safety analysis population. Tables 11 and 12 summarize the analysis populations for year 1 and year 2.

Table 11. Number (%) of Patients in the Year One Populations

Number of Patients in Population	Placebo tid	Orlistat 120 mg tid	Total
Randomized	224	668	892
Safety	223 (99.6%)	664 (99.4%)	887 (99.4%)
Intent-To-Treat	223 (99.6%)	657 (98.4%)	880 (98.7%)
Intent-To-Treat (≥ 12 weeks)	203 (90.6%)	604 (90.4%)	807 (90.5%)
Standard Efficacy	198 (88.4%)	595 (89.1%)	793 (88.9%)
Completer's	133 (59.4%)	429 (64.2%)	562 (63.0%)

Table 12. Number (%) of Patients in the Year Two Populations

Number of Patients	Placebo/ Placebo	120mg/ Placebo	120mg/ 60mg	120mg/ 120mg	Total
Continued from Year One	133	138	152	153	576
Safety	124 (93.2%)	137 (99.3%)	147 (96.7%)	149 (97.4%)	557 (96.7%)
ITT	122 (91.7%)	136 (98.6%)	145 (98.6%)	147 (96.1%)	550 (95.5%)
ITT (> 60 weeks)	120 (90.2%)	134 (97.1%)	138 (90.8%)	146 (95.4%)	538 (93.4%)
Standard Efficacy	114 (85.7%)	123 (89.1%)	126 (82.9%)	133 (86.9%)	496 (86.1%)
Completer's	80 (60.2%)	78 (56.5%)	83 (54.6%)	88 (57.5%)	329 (57.1%)

A total of 296 (33%) patients withdrew prematurely during year one. There was significant difference between the year one treatment groups ($p=0.06<0.1$). Tables 13 and 14 display the summary of reasons for premature withdrawal.

Table 13. Summary of Reasons for Premature Withdrawal - Year One

Reasons	Placebo		Orlistat 120 mg	
	n	(%)	n	(%)
Adverse Event	9	(4.0%)	61	(9.1%)
Treatment Failure	11	(4.9%)	6	(0.9%)
Refused Treatment	2	(0.9%)	0	
Lost to follow-up	21	(9.4%)	59	(8.8%)
Did not cooperate	16	(7.1%)	26	(3.9%)
Protocol violation	5	(2.2%)	13	(1.9%)
Entry violation	1	(0.4%)	3	(0.4%)
Administrative	21	(9.4%)	42	(6.3%)
Total	86	(38.4%)	210	(31.4%)

Table 14. Summary of Year Two Withdrawals

Reasons	Pla/Pla		120mg/Pla		120mg/60mg		120mg/120mg	
	n	(%)	n	(%)	n	(%)	n	(%)
Adverse Event	4	(3.0%)	6	(4.3%)	9	(5.9%)	5	(3.3%)
Treatment Failure	3	(2.3%)	6	(4.4%)	4	(2.6%)	3	(2.0%)
Refused Treatment	3	(2.3%)	0	(0%)	2	(1.3%)	2	(1.3%)
Died during study	1	(0.8%)	0	(0%)	0	(0%)	0	(0%)
Lost to follow-up	15	(11.3%)	15	(10.9%)	22	(14.5%)	17	(11.1%)
Did not cooperate	5	(3.8%)	4	(2.9%)	6	(3.9%)	6	(3.9%)
Protocol violation	3	(2.3%)	6	(4.3%)	5	(3.3%)	3	(2.0%)
Entry violation	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Administrative	2	(1.5%)	6	(4.3%)	2	(1.3%)	8	(5.2%)
Total	36	(27.1%)	43	(31.2%)	50	(32.9%)	44	(28.8%)

The demographic characteristics at the start of the placebo lead-in were similar. The majority of patients were white (81%) and female (84%) with 14% black, and 4% Hispanic. The mean age was 43.4 years, with a mean BMI at day -28 of 36.2 kg/m². At year 2,

the 120 mg/60 mg group had a slightly higher proportion of males (22%) than the other three treatment groups (12% to 17%).

Efficacy Results:

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The year one (baseline to week 52) analysis, the year two (start of 2nd year to week 104) analysis on patients treated with orlistat 120 mg in the first year and the two-year analysis (baseline to week 104) were planned analyses of the sponsor. There was also an unplanned analysis which compares patients on the same treatment for two years (120 mg orlistat vs. Placebo).

The baseline mean weight and mean BMI by stratum is displayed in Table 15.

Table 15. Baseline Mean Weight and BMI by Treatment and Stratum

Stratum	n	Baseline			
		Orlistat Wt. (SD)	BMI (SD)	Placebo n	Wt. (SD) BMI (SD)
1	293	99.0 (14.7)	35.87 (3.77)	104	99.7 (14.5) 35.94 (3.63)
2	364	97.9 (14.5)	34.89 (3.58)	119	97.2 (12.9) 35.41 (3.24)
Overall	657	98.4 (13.7)	35.33 (3.70)	223	98.4 (14.6) 35.66 (3.43)

The least squares means of change from baseline, percent change from baseline and BMI change from baseline is in the following table:

Table 16. LSM of Change from Baseline - Year One Analysis

Kg	Stratum	Orlistat	Placebo	Difference from Placebo (95% C.I.)
	1		-2.8	-0.2
2		-6.1	-3.2	-3.0 (-4.2, -1.7)
Overall		-4.4	-1.7	-2.7 (-3.6, -1.8) p=0.0001
%	1	-2.9%	-0.3%	-2.6% (-4.0%, -1.3%)
	2	-6.4%	-3.3%	-3.1% (-4.3%, -1.8%)
	Overall	-4.6%	-1.8%	-2.9% (-3.8%, -1.9%) p=0.0001
BMI	1	-1.02	-0.09	-0.93 (-1.42, -0.45)
	2	-2.21	-1.18	-1.03 (-1.48, -0.59)
	Overall	-1.62	-0.64	-0.98 (-1.31, -0.66) p=0.0001

The two years weight change from baseline to the end of week 104

for all four treatment groups is displayed in Table 17 for the ITT and "completers" populations.

Table 17. LSM Weight Change (kg) from Baseline to the End of Week 104 for All Treatment Groups

Population Treatment	n	LSM Change from Baseline	Difference from Placebo (C.I.)	P-value
ITT				
Pla/Pla	122	-0.52		
120/Pla	136	-0.77	-0.24 (-2.15, 1.66)	0.801
120/60	145	-2.16	-1.64 (-3.44, 0.16)	0.074
120/120	147	-2.39	-1.87 (-3.68, -0.05)	0.044
Completers				
Pla/Pla	80	-2.29		
120/Pla	75	-1.03	1.26 (-1.71, 4.23)	0.404
120/60	78	-2.49	-0.20 (-3.03, 2.63)	0.888
120/120	86	-3.50	-1.21 (-3.88, 1.46)	0.374

The year two weight change from start of the second year treatment to the end of week 104 is in Table 18.

Table 18. LSM Weight Change (kg) from Week 52 to Week 104 in Year One Orlistat 120 mg Treated Patients

Population Treatment	n	LSM Change from 2nd year Baseline	Difference from Placebo (C.I.)	P-value
ITT				
120/Pla	136	5.16		
120/60	145	3.39	-1.77 (-2.80, -0.73)	0.001
120/120	147	3.20	-1.95 (-2.99, -0.92)	0.000
Completers				
120/Pla	78	5.49		
120/60	83	4.21	-1.28 (-2.81, 0.24)	0.098
120/120	88	3.03	-2.46 (-3.99, -0.94)	0.002

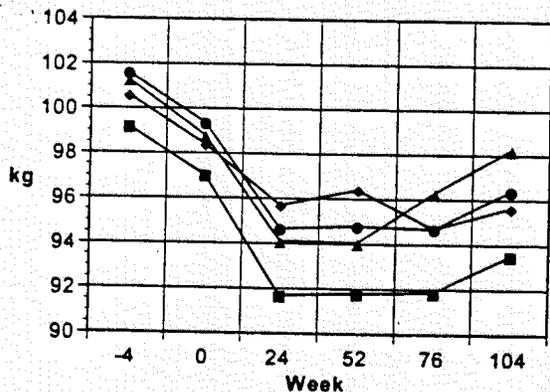
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When comparing patients on the same treatment (120/120 vs Pla/Pla) for two years, the analysis of variance on change of weight from baseline to year two showed that the LOCF analysis with 122 patients in the placebo group and 147 patients in the 120mg/120mg orlistat group had a p-value of 0.041 with a LSM difference of -2.04kg (C.I., -4.01, -0.08). The observed cases of the ITT population which had 89 patients in the placebo group and 101 patients in the 120 mg tid group was not significantly different between treatment groups with p=0.21 and the least squares difference from Placebo/Placebo group was -1.73 kg(-2.43 vs. -0.70) (C.I., -4.44, 0.97).

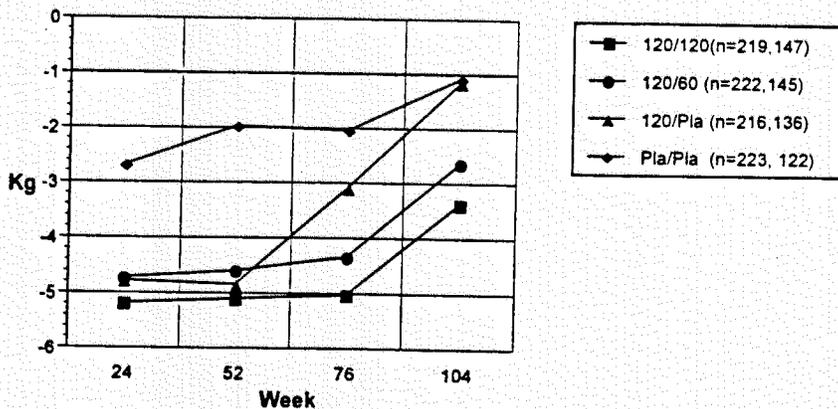
The mean weight over time and mean change in weight from baseline over time in the LOCF of the ITT population is displayed in the following figures. The legend shows treatment group with different sample sizes from year 1 to year 2. In this analysis the sponsor noted that Center USA10165 was deleted from the observed cases of ITT population at the Week 104 time point because of missing cell complication.

Figure 8. Mean Weight and Mean Change of Weight from

Study 14185-Mean Weight from Screen to year 2, ITT with LOCF



Study 14185-Mean Change of Weight from Baseline over Time, LOCF-

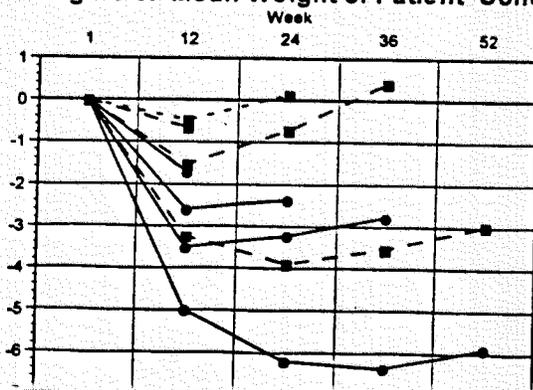


■	120/120(n=219,147)
●	120/60 (n=222,145)
▲	120/Pla (n=216,136)
◆	Pla/Pla (n=223,122)

120/120	99.2	97.0	91.7	91.8	91.9	93.5
120/60	101.	99.4	94.7	94.8	94.7	96.4
120/Pla	101.	98.8	94.1	94.0	96.3	98.2
Pla/Pla	100.	98.4	95.7	96.4	94.7	95.6

120/120	-5.18	-5.09	-5.02	-3.38
120/60	-4.72	-4.59	-4.34	-2.64
120/Pla	-4.77	-4.84	-3.09	-1.14
Pla/Pla	-2.68	-1.97	-2.03	-1.07

Figure 9. Mean Weight of Patient Cohorts



Baseline to Year 2.

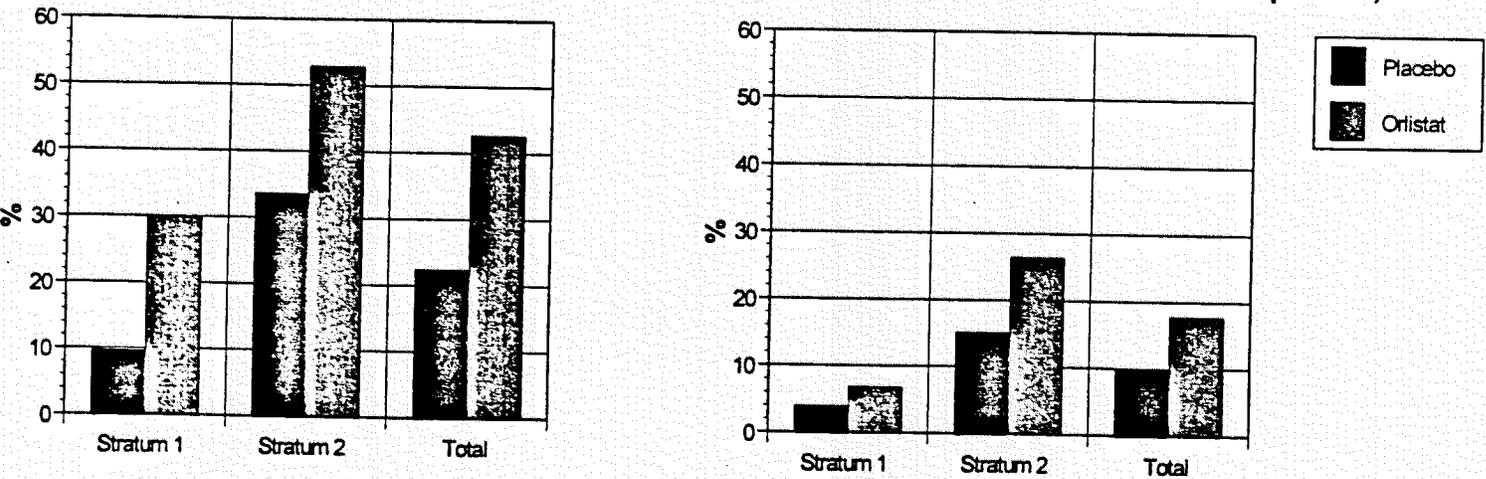
The responder analysis on the proportion of patients who lost 5% or more by stratum and treatment and 10% or more are displayed in Table 19. The Cochran-Mantel-Haenszel Statistics is significant at $\alpha=0.001$ for the 5% responder analysis and $\alpha=0.006$ for the 10% responder analysis. The results were similar when the analyses were stratified by center.

Table 19. Percentage of Patients who lost $\geq 5\%$ and $\geq 10\%$ from Baseline by Stratum - ITT Population

	Placebo $\geq 5\%$	Orlistat $\geq 5\%$	Placebo $\geq 10\%$	Orlistat $\geq 10\%$
Stratum 1 (lead-in ≤ 2 Kg)	9.6% (10/104)	30.0% (88/293)	3.9% (4/104)	6.8% (20/293)
Stratum 2 (lead-in > 2 Kg)	33.6% (40/119)	52.8% (192/364)	15.1% (18/119)	26.4% (96/364)
Total	22.4% (50/223)	42.6% (280/657)	9.9% (22/223)	17.7% (116/657)

Figure 10. Percentage of Responders of 5% and 10% at Year 1

Study M14185- Proportion of 5% Responder, ITT Study M14185- Proportion of 10% Responder, ITT



Adverse Events

Year One

The orlistat 120 mg patients experienced a significantly higher incidence (80.9%) in gastrointestinal (GI) adverse events than the placebo patients (66.4%). The incidence of severe adverse events was higher in the orlistat group (17%) than the placebo group (14%) which is primarily caused by greater frequency of severe episodes of certain gastrointestinal adverse events (oily spotting, flatus with discharge, fecal urgency and fecal incontinence) among orlistat patients. There

were 7.2% of the placebo patients and 47.7% of the orlistat patients whose adverse events are probable (strongest relationship) related to the treatment. The percentage of patients with adverse events by intensity and relationship to treatment is displayed in Table 20.

Table 20. Year One Percentage of Patients with Adverse Events

	Placebo n=223		120mg Orlistat n=664	
	n	%	n	%
Severity				
Mild	81	(36.3%)	177	(26.7%)
Moderate	101	(45.3%)	347	(52.3%)
Severe	31	(13.9%)	113	(17.0%)
Relation to Test Drug				
Unrelated	86	(38.6%)	116	(17.5%)
Remote	36	(16.1%)	28	(4.2%)
Possible	75	(33.6%)	176	(26.5%)
Probable	16	(7.2%)	317	(47.7%)
Total #. of Patients with Adverse Event	213	(95.5%)	637	(95.9%)

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Year Two

There was a higher incidence of gastrointestinal adverse events in the 120mg/120mg group (51%) compared to the other three treatment groups (42% to 45%) caused by slightly higher frequencies of flatulence, oily spotting, increased defecation and oily evacuation episodes among patients treated with 120 mg orlistat during year two. The percentages of patients with adverse events probable (strongest) related to test drug in year two were 2% among placebo patients, 8% among 60 mg orlistat patients and 17% among 120 mg orlistat patients as the following table indicated.

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Table 19. Year Two Percentage of Patients with Adverse Events

	Pla/Pla n=124		120/120 n=149		120/Pla n=137		120/60 n=147	
	n	%	n	%	n	%	n	%
Severity								
Mild	48	(38.7%)	59	(39.6%)	53	(38.7%)	54	(36.7%)
Moderate	56	(45.2%)	52	(34.9%)	61	(44.5%)	56	(38.1%)
Severe	7	(5.6%)	16	(10.7%)	10	(7.3%)	17	(11.6%)
Relation to Test Drug								
Unrelated	86	(38.6%)	56	(37.6%)	77	(56.2%)	75	(51.0%)
Remote	36	(16.1%)	17	(11.4%)	17	(12.4%)	17	(11.6%)
Possible	75	(33.6%)	29	(19.5%)	27	(19.7%)	23	(15.6%)
Probable	16	(7.2%)	25	(16.8%)	3	(2.2%)	12	(8.2%)
Total # of Patients with Adverse Event	111	(89.5%)	127	(85.2%)	124	(90.5%)	127	(86.4%)

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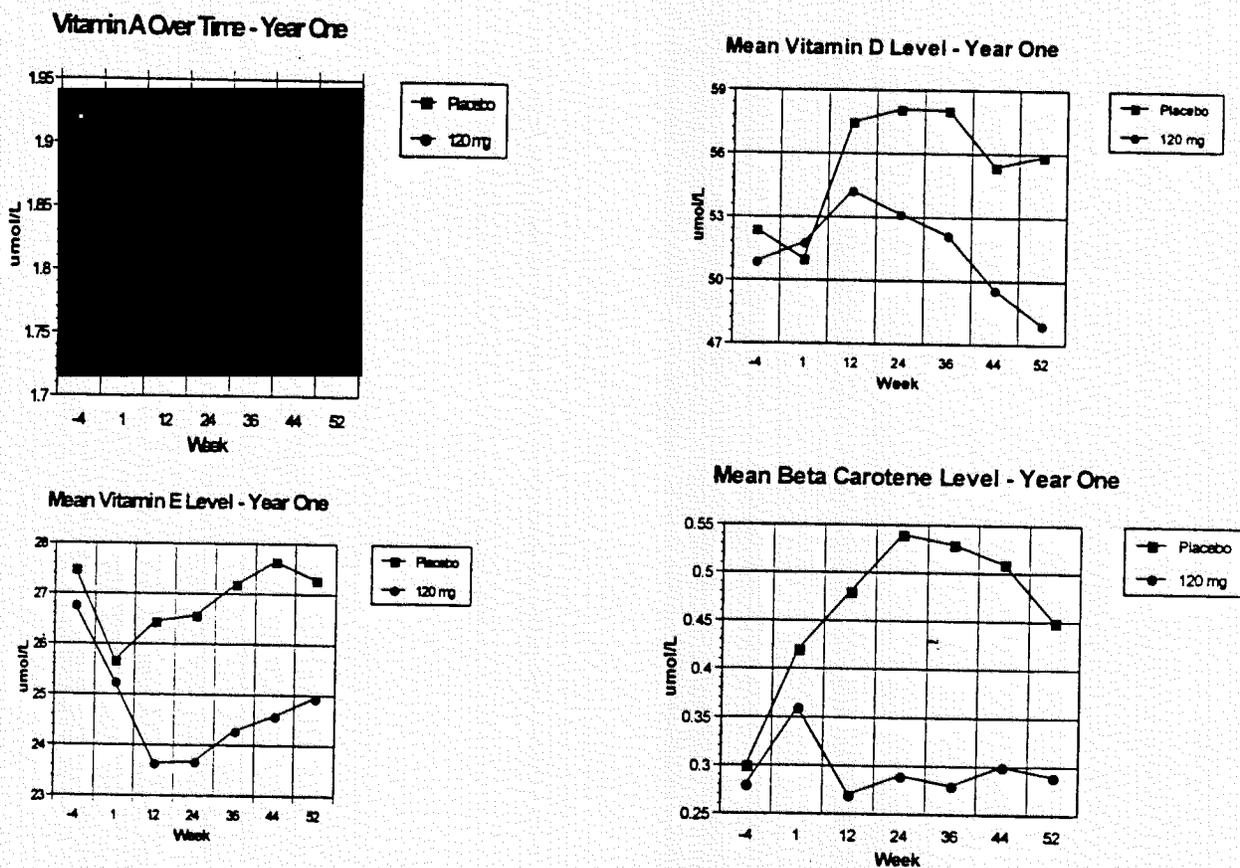
Vitamins

The least squares mean of change in vitamins at year 1 is displayed in Table 20.

Table 20. Least Squares Mean of Change in Vitamins at End of 52 Weeks of Double-Blind Treatment, ITT

	n	Baseline	LSMean Change from Baseline (difference from placebo)	p-value
Vitamin A				
Placebo	216	1.72	0.13	
120 mg	629	1.77	0.10 (-0.03)	0.309
Vitamin D				
Placebo	216	51.17	2.09	
120 mg	630	51.37	-1.47 (-3.56)	0.013
Vitamin E				
Placebo	216	25.67	1.58	
120 mg	629	25.25	-0.46 (-2.04)	0.000
β -Carotene				
Placebo	216	0.42	0.03	
120 mg	629	0.37	-0.09 (-0.12)	0.000

Figure 11. Serum Vitamin Levels



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Serum Lipid

After one year of treatment, the percent changes from baseline for Total Cholesterol, LDL and HDL were significantly different between orlistat and placebo. For HDL, the least squares mean increase of placebo is 10.91% and for the orlistat patients the increase is 7.04%. The analyses of percent change of lipids are displayed in Table 23.

Table 23. LSM Percent Change from Baseline of Lipid

	n	Baseline	LSMean %Change from Baseline (difference from placebo)	p-value
Total Cholesterol				
Placebo	204	4.96	6.00	
120 mg	609	4.90	-1.72 (-7.73)	0.000
LDL				
Placebo	202	3.16	3.84	
120 mg	606	3.08	-4.61 (-8.45)	0.000
HDL				
Placebo	204	1.21	10.91	
120 mg	609	1.17	7.04 (-3.87)	0.002
Triglycerides				
Placebo	204	1.40	7.27	
120 mg	609	1.53	2.28 (-4.98)	0.091

The Pearson's correlation coefficient between weight change and the lipid change of the two treatment groups are displayed in Table 24.

Table 24. Correlation between Weight Change and Lipid Change

	n	Mean Change from Baseline	ρ	p-value $H_0: \rho=0$
Total Cholesterol				
Placebo	204	0.27	-0.02	0.813
120 mg	609	-0.11	0.16	0.0001
LDL				
Placebo	202	0.10	0.02	0.770
120 mg	606	-0.17	0.15	0.0001
HDL				
Placebo	204	0.12	-0.34	0.0001
120 mg	609	0.07	-0.18	0.0001
Triglycerides				
Placebo	204	0.07	0.15	0.032
120 mg	609	-0.02	0.24	0.0001

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Subgroup Analysis in Gender, Race and Age
The mean change in weight from baseline to year 1 for males and females are displayed in Table 25.

Table 25. Subgroup Analysis with Treatment-by-Subgroup Interaction

Subgroup	120 mg n	Mean (Kg)	Placebo n	Mean	Difference from Placebo (Treatment*Subgroup p-value)
Gender					
Male	113	-4.24	26	-1.07	-3.17 -2.88 (p=0.84)
Female	544	-4.96	197	-2.08	
Race					
White	177	-2.28	534	-5.11	-2.83 -2.80 (p=0.98)
Black	35	-1.05	88	-3.85	

The treatment-by-age interaction is not significant (p=0.2).

Conclusion:

With the ITT population after one year of double-blind treatment, the least squares mean weight lost from baseline with LOCF for the orlistat 120 mg tid patients (n=657) was 4.4 kg and for the placebo group (n=223) it was 1.7 kg (p=0.0001). The difference from placebo

with a 95% confidence interval was 2.7 kg (1.8kg, 3.6kg). In the responders analysis of percentage of patients with 5% or more weight lost from baseline weight, 42.6% of the orlistat 120 mg tid patients and 22.4% of the placebo patients were responders (p=0.001). The percentages of patients who lost at least 10% from baseline weight were 17.7% and 9.9%, respectively for orlistat 120 mg and placebo (p=0.006).

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